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The Challenges of First-in-Human Stem Cell Clinical Trials: What Does This Mean for Ethics and Institutional Review Boards?

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Stem cell-based clinical interventions are increasingly advancing through preclinical testing and approaching clinical trials. The complexity and diversity of these approaches, and the confusion created by unproven and untested stem cell-based “therapies,” create a growing need for a more comprehensive review of these early-stage human trials to ensure they place the patients at minimal risk of adverse events but are also based on solid evidence of preclinical efficacy with a clear scientific rationale for that effect. To address this issue and supplement the independent review process, especially that of the ethics and institutional review boards who may not be experts in stem cell biology, the International Society for Stem Cell Research (ISSCR) has developed a set of practical questions to cover the major issues for which clear evidence-based answers need to be obtained before approving a stem cell-based trial.

In recent years, the number of clinical trials and range of medical conditions being tested with stem cell-derived interventions has expanded. The complexity and diversity of these putative therapies, and their use in early-stage human trials, pose unique review challenges relative to those required for pharmacological agents, which includes the delivery of the therapy and the possible mode of function. Unfortunately, the field has become increasingly confounded by the desire to rapidly move some stem cell-derived interventions to the clinic without sufficient scientific rationale to support this approach, including growing numbers of direct-to-consumer, incompletely tested, or even untested, “cell therapies.” The latter, untested, putative therapies are often described as trials even though the patient is required to pay for the experimental treatment, an atypical approach that raises ethical concerns. In addition, these “trials” are often registered on a clinical trials website, such as clinicaltrials.gov, a common tactic to convey legitimacy, even though simply being listed on such sites offers no guarantees about the level of scientific scrutiny that they have undergone. Consequently, institutional review and ethics boards, physicians, scientists, and especially patients, struggle to understand which of these

interventions has sufficient merit to justify clinical evaluation. By their very nature, cell-based interventions require more comprehensive evaluation to ensure they have a justified level of risk for the recipient, are based on solid preclinical evidence of efficacy, and a clear scientific rationale for that effect. This call for a greater emphasis on preclinical data and rationale has been echoed by others for early human trials (Kimmelman and Federico, 2017). This need for a comprehensive, independent review is likely to become more of an issue as the number of trials and conditions that could be treated with stem cell-derived interventions increases. Indeed, the volume of trials could dramatically expand if, and when, regulatory agencies require that direct-to-consumer interventions undergo a formal regulatory review. This welcome change would further increase the need for ethics and institutional review boards to be highly engaged and informed.

Therefore, it has become imperative to improve on the evaluation of stem cell therapies, especially in first-in-human studies, to distinguish between:

- (1) Trials with justified merit and potential that are supported by strong scientific rationale; and
- (2) Trials that do not have adequate preclinical safety and efficacy testing and may therefore endanger patients and jeopardize the whole field of regenerative medicine.

One way to enhance this process is to more fully engage an independent ethics or institutional review board. These key stakeholders need not be experts in stem cell biology to make reasonable judgments about whether the preclinical evidence justifies a clinical trial and/or whether such an approved trial is appropriate to undertake at their institution(s). We submit that knowing a few basic facts about stem cells, understanding fundamentals of preclinical testing and clinical trial design, and good common sense are sufficient. Toward that end, the ISSCR has developed





a framework of questions that can be asked, some of the key points of which are highlighted below.

The first consideration is whether the condition to be treated is a disease of cellular deficiency. These are the diseases for which stem cell-derived interventions have the most logical application. In this context, stem cells have two general mechanisms of action: direct integration to replace the damaged tissue (“cellular replacement”), and indirect signaling to host tissues (“paracrine repair”). To regenerate the tissue through cellular replacement, stem cell derivatives must engraft in the tissue and survive long term. Consequently, this modality requires long-term monitoring of the patient. In paracrine repair, the cells are typically delivered into systemic compartments, such as the circulation or CSF, as they likely work via transient signaling mechanisms. In this case, the mechanism of action is typically less well defined but can include reducing inflammation and scarring in addition to promoting cell survival, or proliferation of endogenous cells, and/or angiogenesis. Therapies that cannot provide a clear mechanistic basis or reasonable rationale, and that lack preclinical evidence of efficacy, proof of concept, and safety, are unlikely to be ready for clinical trials.

In addition to how the cells are thought to work and their mode of delivery, the immunological relationship between the transplanted cells and the patient is important. In most cases the intervention involves allogeneic cells and so immune suppression may be needed to prevent rejection or, in the case of hematopoietic cell transplantation, immune cells in the graft from attacking host tissues, as in graft-versus-host disease. Grafts in the CNS and eye may be an exception, as immune surveillance is restricted at these sites; yet even then, some form of immunosuppression may be needed, at least in the short term. The risks of immunosuppression thus need to be considered before trial approval or enrollment.

Once the general mechanism of action is understood (cell replacement or paracrine repair), stem cell-based clinical trials should largely follow the precedents already established for the evaluation of small molecules, biologics, and human tissues. Preclinical studies should demonstrate safety and efficacy profiles that suggest improvement over the standard of care. Cell production needs to take place in facilities that follow current Good Manufacturing Practices, with stringent quality control for reagents and well-defined product release and potency assays. Phase 1 trials should begin cautiously, e.g., with dose-escalation protocols and phased enrollments to allow complications to be identified with the fewest possible patients. The design of these early trials will need to balance the safety and efficacy profiles of the stem cell therapy, while assessing the risk tolerance of

specific patient populations. These trials should be properly funded (and not by the patients themselves), focus on tolerability and feasibility, while establishing endpoints to be used in later safety and efficacy trials. When treating solid organs such as the heart or brain, delivery of the cells is a key feature and consideration. Delivery systems such as the use of an intravascular catheter or surgical injection may be required and need to be evaluated during preclinical and clinical testing in concert with the cell product, as they both can influence the safety and efficacy profile of the therapeutic tested. Such considerations also need to be undertaken when the stem cell-derived intervention is combined with other emerging technologies, e.g., gene therapy, which brings with it its own regulatory issues and concerns.

While helpful guidelines have been developed for the clinical translation of stem cell-based interventions, they broadly cover fundamental ethical aspects of stem cell therapies (Daley et al., 2016). Yet for those having to make decisions at the local level, such as ethics and institutional review boards, a more succinct and directed document, such as a simple questionnaire, might be more useful for evaluating new cell therapy treatments and trials. These questions should cover the major issues for which clear evidence-based answers need to be obtained. This approach has been developed by a group of physicians and regulators working with the International Society for Stem Cell Research (ISSCR). The document, “Stem Cell-Based Clinical Trials: Practical Advice for Physicians and Ethics/Institutional Review Boards” (http://www.isscr.org/docs/default-source/clinical-resources/isscr-stem-cell-based-clinical-trials-practical-advice_final_23jan2018.pdf?sfvrsn=2) provides a framework of questions that can engage and empower the key stakeholders involved with the translation of therapies to patients.

The questionnaire is designed to provide practical advice that addresses relevant issues as part of a broader review process. By adopting such a review, those having to make decisions on the potential benefits and safety of any proposed stem cell-derived intervention will be able to ascertain whether there is sufficient support for moving the cell product to a clinical trial, and whether the underlying science and clinical endpoints are reasonable for the patient population and the stage of therapeutic development.

To further support those overseeing the authorization of these trials, additional resources will need to be provided. These may include providing access to experts with whom these issues can be discussed; possibly through establishing a national registry of such individuals, ideally vetted through some already existing agency such as the ISSCR or other reputable organizations. In addition, the sponsor has a responsibility to provide answers to these



questions. While there are significant challenges to establishing such a resource and no immediate mechanism to do so, collectively, this process would support the review process but not prohibitively slow it, allowing trials to proceed at a speed dictated by the science. This will hopefully protect the patients as well as this nascent field, while allowing novel regenerative medicine products that have the potential to transform lives to reach the clinic.

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